Estrogen Replacement Therapy and Breast Cancer Survival in a Large Screening Study

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Background: **Hormone replacement therapy has been associated in some studies with reductions in breast cancer mortality among women who develop this disease. It is unclear whether this association reflects the biologic activity of the hormones or the earlier detection of tumors among hormone users. We examined breast cancer mortality among women who were diagnosed with axillary lymph node-negative and node-positive breast cancer according to the currency of estrogen use at diagnosis.** ***Methods:*** **Vital status through June 1995 was determined for 2614 patients with postmenopausal breast cancer diagnosed during the period from 1973 to January 1981. We estimated adjusted hazard-rate ratios (adjusting for tumor size, age, race, Quetelet [body mass] index, and number of positive lymph nodes in women with node-positive disease) and unadjusted cumulative probabilities of breast cancer death over time since diagnosis.** ***Results:*** **Among patients with node-negative disease, rate ratios for breast cancer mortality associated with current use compared with nonuse at diagnosis were 0.5 (95% confidence interval [CI] = 0.3–0.8) until 144 months after diagnosis and 2.2 (95% CI = 0.9–5.2) thereafter. Mortality was not statistically significantly lower in past users. The cumulative probabilities of breast cancer mortality at the end of follow-up were 0.14, 0.14, and 0.09 in nonusers, past users, and current users, respectively. Among women with node-positive disease, the rate ratios associated with current and past use were both 0.5 until 48 months after diagnosis (95% CI = 0.3–0.8 for current users; 95% CI = 0.3–0.9 for past users) and were 1.1 (95% CI = 0.7–1.7) and 1.8 (95% CI = 1.2–2.7), respectively, thereafter. The cumulative probabilities of breast cancer mortality were 0.32, 0.39, and 0.27 in nonusers, past users, and current users, respectively.** ***Conclusions:*** **Patients with breast cancer who were using replacement estrogens at the time of diagnosis experienced reductions in breast cancer mortality, which waned with the time since diagnosis. [J Natl Cancer Inst 1999;91:264–70]**

Although hormone replacement therapy is associated with an increased incidence of breast cancer *(1)*, it has been associated with lower mortality from breast cancer or improved survival after a diagnosis of breast cancer in some *(2–11)*, but not all *(12–16)*, studies. The observation that hormones preferentially increase the risk of developing less advanced tumors *(1)* raises the possibility that the lower mortality in hormone users reflects increased breast cancer surveillance, rather than a biologic effect of hormones. Clarification of the role of exogenous hormones on breast cancer prognosis is important both for further understanding of the role of hormones in the carcinogenic process and for weighing the risks and benefits of hormone replacement therapy *(17)*.

To address further the relationship between hormone replacement therapy and breast cancer survival, we examined death from breast cancer according to currency of hormone use at diagnosis among 2614 breast cancer cases diagnosed during the period from 1973 to January 1981 and followed for vital status through June 1995.

Subjects and Methods

Study Subjects

Study subjects were participants in the Breast Cancer Detection Demonstration Project (BCDDP), a 5-year breast cancer screening program sponsored by the National Cancer Institute and the American Cancer Society. Conducted during the period from 1973 through 1980, the BCDDP involved more than 280 000 women at 29 centers in 27 cities throughout the United States. Five annual examinations, each including a physical examination of the breast and mammography, were offered to each screening participant. A total of 4363 breast cancers were detected among the screening participants during the 5-year course of the project.

In 1980, at the end of the BCDDP, the National Cancer Institute initiated a follow-up study that included, among others, all patients with breast cancer that had been diagnosed during the BCDDP. The follow-up study included yearly telephone interviews until 1986 and continued with two self-administered, mailed questionnaires, the first during the period from 1987 through 1989 and the second during the period from 1993 through June 1995. We made vigorous efforts to locate and obtain the vital status of all participants in the follow-up study, which included a search of the National Death Index through 1993. The follow-up study was approved by the Institutional Review Board at the National Cancer Institute.

Data

We limited our analysis to women whose first diagnosis of breast cancer occurred during the BCDDP and who were menopausal at the time of diagnosis (n = 2675). We ascertained vital status through the last mailing of questionnaires (in 1995). A total of 1039 women died during the follow-up period from 1974 through June 1995. For the 1636 women who did not die during the follow-up period, we ascertained vital status for 2.6% through 1992, for 34.8% through 1993, for 57.5% through 1994, and for 5.2% into 1995. We obtained death certificates for 97.7% of the identified deaths, allowing us to code cause of death. We excluded 61 subjects whose death certificates were not available, leaving an analytic dataset of 2614 women. A total of 486 deaths from breast cancer and 492 deaths from causes other than breast cancer were identified during follow-up among these study subjects.

Data Sources

We obtained information on female hormone use and other breast cancer risk factors from the following sources: 1) questionnaires completed at each of the five annual screening visits of the BCDDP; 2) an in-home interview administered as part of a case–control study involving breast cancer cases diagnosed during the BCDDP, which was completed by 72.3% of the 2614 members of the analytic cohort *(18)*; and 3) telephone interviews administered as part of the follow-up study, which were completed by 87% of the analytic cohort.

Exposure Definitions

Information on the noncontraceptive use of female hormones was available from all three data sources listed above. Only the case–control interview, however, elicited details on the type, name, and dose of hormones used in relationship to menopause. Among patients with breast cancer included in the case–control study who used hormones, 1.25 mg of Premarin was the preparation used longest by 40%, 0.625 mg of Premarin was the preparation

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See "Note" following "References."

used longest by 17%, other doses of Premarin were the preparations used longest by 15%, diethylstilbestrol was the preparation used longest by 4%, and other hormones were the preparations used longest by 9%. Fourteen percent of patients who used hormones were uncertain of the type of hormone used longest *(18)*. Progestins were not prescribed widely in the 1970s when these women were diagnosed with breast cancer.

Information on current, past, or never use of hormones at the time of breast cancer diagnosis was available for 94.7% of the study subjects. For 76.4% of the subjects, the currency of hormone use was based on the BCDDP screening form completed within a year before breast cancer diagnosis. Some subjects were administered versions of these forms that ascertained currency of hormone use but did not distinguish between past use and never use of hormones. For the 14.1% of study subjects who reported on one of these forms that they were not currently using hormones, information from the case–control and follow-up interviews was used to separate past users from never users. Similarly, for the 9.5% of study subjects for whom currency of use was unknown on the basis of the screening forms (for instance, some subjects did not have a screening form within a year of diagnosis), information from the available case–control and follow-up interviews was used to determine currency of use. Status of hormone use was not defined for 61 women who died of breast cancer (12.6% of breast cancer case patients), for 31 women who died of other causes (6.3% of other causes of death), and for 48 women who did not die during the follow-up period (2.9% of surviving case patients).

Information on duration of hormone use was available from the case–control or follow-up interview for 65% of hormone users. Information on time since last use was available for 76% of past users.

We determined menopausal status at the time of breast cancer diagnosis from information obtained at the case–control interview, from the baseline interview of the follow-up study, or from the most recent screening form that was obtained prior to the diagnosis of breast cancer (in that order of preference). This hierarchical scheme was used because the case–control interview provided the most detailed information on menopausal status and the screening forms provided the least. The following women were included in the analysis if their age at diagnosis was at least 1 year greater than the age at their last reported period: 1) women who stopped menstruating because of removal of both ovaries, 2) women who stopped menstruating because of a hysterectomy if their age at surgery was greater than the median age at natural menopause in this cohort (51.1 years), 3) women who reported a natural menopause (defined as not having a period for 3 months), and 4) the 281 women (11%) without a case–control or follow-up interview if they reported no longer having regular periods on the closest screening form prior to their date of diagnosis.

Information on tumor size and axillary lymph node status was available from standardized pathology reports obtained for 95% of study subjects as part of the BCDDP *(19)*. No information was available on presence of distant metastases. We designated extent of disease as follows: *in situ* (both lobular and ductal); lymph node-negative with tumor sizes of less than 2 cm, 2 cm or more and less than 5 cm, or 5 cm or more; and lymph node-positive with tumor sizes of less than 2 cm, 2 cm or more and less than 5 cm, or 5 cm or more.

We classified the histology of invasive tumors into the following five categories: 1) carcinoma of the breast with productive fibrosis, carcinoma of the breast (not otherwise specified), metaplastic mammary carcinoma, or minimally invasive infiltrating duct cell carcinomas; 2) medullary or lobular carcinoma; 3) comedo or papillary carcinoma; 4) mucinous or tubular carcinoma; and 5) unknown histology *(20)*. For cases with multiple histologies, the lowest numbered category was used.

We obtained demographic information from forms filled out upon entry into the screening program, and we obtained information on height and weight from the form completed at the closest screening visit before the diagnosis of breast cancer. The Quetelet (body mass) index was calculated as weight in kilograms divided by height in square meters.

Statistical Analyses

Death from breast cancer, determined from the underlying cause of death on the death certificate [International Classification of Diseases for Oncology codes 1748 or 1749 *(21)*], was the primary outcome of interest. We considered deaths from causes other than breast cancer to be competing risks. We censored survival time at the date of death or the date of last interview or contact.

We used Cox proportional hazards models to obtain univariate and multivariate hazard rate ratio estimates of death from breast cancer associated with hormone use and other factors *(22)*. The time scale was months after a breast cancer diagnosis. We assessed the appropriateness of the proportional hazards model by testing the significance of an interaction term between covariates and time in the proportional hazards model. Because we found significant evidence of nonproportionality of the hazards for groups defined by age at diagnosis, we stratified by age at diagnosis in the proportional hazards models. Hormone use, the primary exposure of interest, also did not satisfy the proportional hazards assumption over the entire period of follow-up. Therefore, we calculated hazard rate ratios for different time periods since diagnosis to evaluate the effects of hormone exposure.

To determine proportions of study subjects dying of breast cancer according to hormone use, we calculated cumulative crude probabilities of death from breast cancer by time t in the presence of competing risks, unadjusted for other prognostic factors *(23)*. The statistical significance of the differences in the cumulative probability among exposure groups was derived from statistics based on cumulative weighted differences, as in the paper by Pepe and Mori *(23)*. These probabilities are observable quantities that reflect the effect of an exposure on competing causes of death as well as the cause of death of interest. To put confidence intervals (CIs) on estimated cumulative crude probabilities of death from breast cancer, we applied counting process methods to calculate the variance of quantities $U_{P_R}^i$, defined in the paper by Pepe and Mori *(23)*.

We calculated the median time to death among those who had died of breast cancer by the end of the study period from the distribution of the ratio of the cumulative probability of dying of breast cancer by time t and the cumulative probability of dying of breast cancer at the end of the follow-up period *(24)*.

We used software developed by Pepe and Mori *(23)* to calculate crude probabilities. We used standard chi-squared tests to evaluate associations in contingency tables, and we used the notation χ^2 (df) to denote a chi-squared distribution with degrees of freedom (df) *(25)*. All *P* values are two-sided and were considered statistically significant for $P<.05$.

Results

Subjects were followed, on average, for 14.1 years after a diagnosis of breast cancer. The median follow-up time was 16.0 years, with a maximum of 21.3 years and a minimum of less than a year. A total of 978 deaths occurred among the 2614 study subjects, including 486 deaths from breast cancer.

Prognostic Factors

Table 1 presents hazard ratios for potential prognostic factors for breast cancer survival, adjusted for other factors in the table. As expected, the extent of disease at diagnosis was a very strong prognostic factor, as was the number of positive lymph nodes in lymph node-positive women. Patients with mucinous or tubular invasive tumors were at lower risk than those with invasive tumors of other histologic types. Breast cancer mortality was greater in patients with a high body mass index, with those in the highest compared with the lowest quartile having a 60% excess mortality. Blacks and those of other races were at 70% higher risk than whites.

Hazard rates associated with age were not proportional over the follow-up period; women 55 years of age and older were at reduced risk of death from breast cancer compared with younger women for the first 48 months since diagnosis but were at higher risk after 144 months since diagnosis (data not shown). Level of income, educational level, and marital status were not prognostic factors before or after adjustment for other variables.

As shown in Table 2, current users of hormones were more likely to have been diagnosed with *in situ* tumors than nonusers ($P = .001$, χ^2 test, df = 18). There were no remarkable differences in other tumor characteristics according to hormone use. A higher proportion of current users had a lower body mass index than nonusers or past users ($P<.0001$, χ^2 test, df = 8), were white ($P = .0005$, χ^2 test, df = 8), and were younger at diagnosis ($P<.0001$, χ^2 test, df = 12).

Table 1. Hazard ratios (HRs) indicating effect of selected characteristics on breast cancer mortality rates following diagnosis*

Characteristic	No. of breast cancer deaths	HR (95% CI)
Extent of disease at diagnosis†		
In situ	8	1.0 (referent)
Node–/<2 cm	73	3.8 (1.8–7.9)
Node–/2–4 cm	71	8.8 (4.3–18.4)
Node–/≥5 cm	22	9.2 (4.1–20.8)
Node+/<2 cm	98	11.5 (5.6–23.7)
Node+/2–4 cm	102	18.2 (8.8–37.4)
Node+/≥5 cm	35	38.4 (17.8–82.9)
Node–/unknown size	39	6.6 (3.1–14.1)
Node+/unknown size	32	8.7 (4.0–18.9)
Unknown	6	1.2 (0.4–3.5)
No. of positive lymph nodes‡		
1	36	1.0 (referent)
2	37	1.2 (0.8–2.0)
3–5	47	1.8 (1.2–2.8)
≥6	96	3.8 (2.6–5.7)
Unknown	51	0.8 (0.5–1.3)
Histology, invasive§		
Ductal	288	1.0 (referent)
Medullary or lobular	57	1.1 (0.8–1.4)
Comedo or papillary	29	1.0 (0.7–1.5)
Mucinous or tubular	7	0.3 (0.2–0.7)
Unknown	97	0.8 (0.6–1.0)
Quetelet index†,‖		
<21.284	62	1.0 (referent)
21.284 to 23.344	103	1.2 (0.9–1.6)
23.344 to 26.152	129	1.3 (0.9–1.7)
>26.152	188	1.6 (1.2–2.1)
Unknown	4	1.3 (0.5–3.7)
Race†		
White	428	1.0 (referent)
Black	39	1.7 (1.2–2.4)
Asian-American	4	0.6 (0.2–1.6)
Other	7	1.7 (0.8–3.6)
Unknown	8	1.3 (0.7–2.7)

*Definitions are as follows: 95% CI = 95% confidence interval; Node– = axillary lymph node negative; Node+ = axillary lymph node positive; Quetelet index (body mass index) = weight in kg/height in m^2.

†Adjusted for the other factors in the table, except histology and number of positive lymph nodes.

‡For case subjects with lymph node-positive disease, adjusted for other factors in the table.

§For case subjects with invasive disease, adjusted for other factors in the table.

‖Strata represent quartiles of body mass index among the case subjects.

Hazard Rates According to Hormone Use

During the follow-up period, 184 of the breast cancer deaths occurred among hormone nonusers at diagnosis, 135 among past users, and 106 among current users. We were unable to determine whether 43 women who died of breast cancer were nonusers or past users, whether 17 were current or past users, and whether one had used hormones at all. Subsequent analyses focus on the subjects who were known to be nonusers, past users, or current users.

Because the hazards associated with nonuse, past use, and current use of hormones were clearly nonproportional over the entire follow-up period and differed in women with lymph node-negative and lymph node-positive breast cancer, we present results according to lymph node status and for different periods of follow-up. Among lymph node-negative women (Table 3, A), including those with *in situ* cancer, current use of hormones compared with nonuse was associated with a 40%–60% reduction in breast cancer mortality rates during the first 144 months since diagnosis and a twofold increase thereafter after adjustment for age at diagnosis, race, Quetelet index, and tumor size. When the first 144 months of follow-up were considered as a single time period, the hazard-rate ratio associated with current use after adjustment for other factors was 0.5 (95% CI = 0.3–0.8). In past users at diagnosis, smaller reductions in breast cancer mortality were evident for the first 96 months after diagnosis; however, thereafter, there were increases that were not statistically significant. When the first 96 months was considered as a single time period, the hazard-rate ratio associated with past use was 0.7 (95% CI = 0.5–1.1).

To provide further assurance that the reduction in mortality associated with current use was not due to greater breast cancer surveillance in hormone users before entering the screening program, we repeated these analyses after eliminating cases detected at the first BCDDP screening visit. Results were essentially unchanged; hazard-rate ratios for current use for the four time periods were 0.6, 0.3, 0.7, and 1.7, and those for past use for the four time periods were 0.6, 0.8, 1.3, and 1.4. Results were also similar when *in situ* cases were excluded and when analyses were limited to invasive cancer with tumor size less than 2 cm.

There were no remarkable differences in these results according to race or levels of Quetelet index. However, results differed according to age at diagnosis. In women less than 60 years old at diagnosis, the hazard-rate ratios for past and current use for the first 144 months since diagnosis were 0.6 (95% CI = 0.4–1.0) and 0.4 (95% CI = 0.2–0.6), respectively; in contrast, in older women, they were 1.0 (95% CI = 0.6–1.8) and 0.7 (95% CI = 0.4–1.4). The attenuation of the protective effect in older women was largely due to a decrease in the hazard rate among older nonusers of hormones, with no corresponding decrease in the hazard rate among current users.

As shown in Table 3, B, current and past hormone use among lymph node-positive women was associated with a 50% reduction in mortality from breast cancer in the first 48 months after diagnosis compared with hormone nonusers—but not thereafter—after adjustment for race, Quetelet index, tumor size, and number of positive lymph nodes. The estimates for past and current use for the entire period after 48 months were 1.8 (95% CI = 1.2–2.7) and 1.1 (95% CI = 0.7–1.7), respectively. Elimination of cases detected during a woman's first screening visit yielded similar results; hazard-rate ratios for current use for the four time periods were 0.4, 0.9, 1.1, and 2.0 and for past use were 0.5, 1.2, 1.3, and 3.8. Results were similar when analyses were limited to those with tumors smaller than 2 cm. Results did not differ substan-

Table 2. Distribution of selected characteristics by hormone use*

Characteristic	Nonusers No.	Nonusers %	Past users No.	Past users %	Current users No.	Current users %
Extent of disease at diagnosis						
In situ	82	8.3	72	10.4	122	15.3
Node–/<2 cm	278	28.3	201	29.1	216	27.1
Node–/2–4 cm	141	14.3	89	12.9	81	10.2
Node–/≥5 cm	39	4.0	32	4.6	22	2.8
Node+/<2 cm	138	14.0	85	12.3	102	12.8
Node+/2–4 cm	99	10.1	60	9.0	64	8.0
Node+/≥5 cm	14	1.4	16	2.3	18	2.3
Node–/unknown size	93	9.5	59	8.5	68	8.5
Node+/unknown size	54	5.5	33	4.8	46	5.8
Unknown	46	4.7	45	6.5	59	7.4
Two-sided $P = .001$, χ^2 test (df = 18)						
No. of positive lymph nodes†						
1 or unknown	164	53.8	94	48.5	129	56.1
2	46	15.1	25	12.9	38	16.5
3–5	44	14.4	38	19.6	22	9.6
≥6	51	16.7	37	19.1	41	17.8
Two-sided $P = .70$, χ^2 test (df = 8)						
Histology‡						
Ductal	501	55.5	345	55.7	341	50.4
Medullary or lobular	77	8.5	56	9.0	76	11.2
Comedo or papillary	48	5.3	38	6.1	33	4.9
Mucinous or tubular	40	4.4	28	4.5	29	4.3
Unknown	236	26.2	153	24.7	197	29.1
Two-sided $P = .34$, χ^2 test (df = 8)						
Quetelet index§						
<21.284	131	13.3	114	16.5	196	24.6
21.284 to <23.344	195	19.8	156	22.5	223	27.9
23.344 to 26.152	264	26.8	198	28.6	217	27.2
>26.152	389	39.5	220	31.8	148	18.6
Unknown	5	0.5	4	0.6	14	1.8
Two-sided $P<.0001$, χ^2 test (df = 8)						
Race						
White	892	90.7	636	91.9	749	93.9
Black	53	5.4	36	5.2	18	2.3
Asian-American	19	1.9	10	1.5	27	3.4
Other	12	1.2	7	1.0	1	0.1
Unknown	8	0.8	3	0.4	3	0.4
Two-sided $P = .0005$, χ^2 test (df = 8)						
Age at diagnosis, y						
<50	70	7.1	27	3.9	81	10.1
50–54	159	16.2	128	18.5	210	26.3
55–59	230	23.4	206	29.8	239	29.9
60–64	205	20.9	160	23.1	170	21.3
65–69	171	17.4	105	15.1	72	9.0
70–74	121	12.3	55	8.0	22	2.8
≥75	26	2.7	11	1.6	5	0.6
Two-sided $P<.0001$, χ^2 test (df = 12)						

*Definitions are as follows: Node– = axillary lymph node negative; Node+ = axillary lymph node positive; df = degrees of freedom; Quetelet index (body mass index) = weight in kg/height in m^2.

†Among lymph node-positive case subjects.

‡Among case subjects with invasive disease.

§Strata represent quartiles of body mass index among the case subjects.

tially according to race, age, or levels of Quetelet index.

Among lymph node-negative women who were current users at diagnosis, duration of use was not associated with risk during the first 144 months since diagnosis; the hazard-rate ratios were 0.3 (95% CI = 0.1–0.7), 0.2 (95% CI = 0.1–0.6), and 0.4 (95% CI = 0.2–0.9) for less than 5 years, 5–9 years, and 10 or more years of use, respectively. Similarly, over the first 96 months since diagnosis, time since last use was not associated with risk among lymph node-negative past users; the hazard-rate ratios were 0.6 (95% CI = 0.3–1.2) for at least 10 years since last use, 0.4 (95% CI = 0.2–1.2) for 5–9 years since last use, and 0.6 (95% CI = 0.3–1.2) for less than 5 years since last use. The data were insufficient to effectively evaluate duration of use and time since last use in lymph node-positive women.

Probabilities of Death From Breast Cancer

In lymph node-negative women, the unadjusted cumulative crude probabilities of death from breast cancer at the end of the follow-up period in nonusers, past users, and current users of hormones were 0.14 (95% CI = 0.12–0.18), 0.14 (95% CI = 0.10–0.18), and 0.09 (95% CI = 0.07–0.12), respectively (P values for the cumulative weighted differences between nonusers and current users and nonusers and past users = .001 and .41, respectively) (Fig. 1, A). At 144 months since diagnosis (until which time hazard rates were lower in current users than in nonusers), the corresponding probabilities were 0.12 (95% CI = 0.10–0.15), 0.10 (95% CI = 0.08–0.13), and 0.06 (95% CI = 0.04–0.08). Ratios of these probabilities for past users compared with nonusers and current users compared with nonusers were 1.0 and 0.6, respectively, at the end of follow-up and 0.8 and 0.5 at 144 months. The median times to death from breast cancer among those who eventually died of breast cancer during the follow-up period were 66 months, 90 months, and 87 months in nonusers, past users, and current users at diagnosis, respectively.

The unadjusted cumulative crude probabilities of death from breast cancer in lymph node-positive women for nonusers, past users, and current users were 0.32 (95% CI = 0.26–0.38), 0.39 (95% CI = 0.31–0.47), and 0.27 (95% CI = 0.22–0.34), respectively (Fig. 1, B). The P values for the cumulative weighted differences between nonusers and current users and nonusers and past users were .18 and .57, respectively. At 48 months after diagnosis (until which time the hazard rate was lower in current and past hormone users than in hormone nonusers), the cumulative probabilities of death were 0.16 (95% CI = 0.13–0.20) in hormone nonusers, 0.09 (95% CI = 0.06–0.14) in past users, and 0.09 (95% CI = 0.6–0.13) in current users. Ratios of crude probabilities at the end of the follow-up period were 1.2 for past users compared with nonusers and 0.8 for current users compared with nonusers. The corresponding ratios at 48 months were 0.6 and 0.6. The median times to death among those who died of breast cancer were 47, 83, and 68 months in nonusers, past users, and current users, respectively.

Table 3. Hazard rate ratios (HRs) of breast cancer mortality according to hormone use and lymph node status

Months since diagnosis	No. of deaths	HR*	HR†	HR‡ (95% confidence interval)
A. Case subjects with lymph node-negative breast cancer				
≤48 mo				
Nonusers	28	1.0	1.0	1.0 (referent)
Past users	14	0.7	0.7	0.8 (0.4–1.4)
Current users	13	0.5	0.6	0.6 (0.3–1.2)
49–96 mo				
Nonusers	35	1.0	1.0	1.0 (referent)
Past users	18	0.7	0.7	0.7 (0.4–1.2)
Current users	11	0.3	0.4	0.4 (0.2–0.8)
97–144 mo				
Nonusers	15	1.0	1.0	1.0 (referent)
Past users	14	1.2	1.2	1.2 (0.6–2.5)
Current users	7	0.5	0.5	0.6 (0.2–1.5)
>144 mo				
Nonusers	9	1.0	1.0	1.0 (referent)
Past users	13	1.8	1.8	1.8 (0.8–4.3)
Current users	13	1.6	1.9	2.2 (0.9–5.2)
Months since diagnosis	No. of deaths	HR*	HR†	HR§ (95% confidence interval)
B. Case subjects with lymph node-positive breast cancer				
≤48 mo				
Nonusers	48	1.0	1.0	1.0 (referent)
Past users	18	0.6	0.6	0.5 (0.3–0.9)
Current users	20	0.5	0.5	0.5 (0.3–0.8)
49–96 mo				
Nonusers	23	1.0	1.0	1.0 (referent)
Past users	26	1.6	1.7	1.6 (0.9–2.8)
Current users	23	1.1	1.2	1.2 (0.6–2.2)
97–144 mo				
Nonusers	18	1.0	1.0	1.0 (referent)
Past users	14	1.2	1.2	1.2 (0.6–2.4)
Current users	10	0.7	0.8	0.8 (0.3–1.7)
>144 mo				
Nonusers	6	1.0	1.0	1.0 (referent)
Past users	15	4.1	4.2	4.4 (1.7–11.8)
Current users	9	1.8	1.9	1.9 (0.6–5.7)

*Adjusted for age.

†Adjusted for age, race, and Quetelet (body mass) index.

‡Adjusted for age, race, Quetelet (body mass) index, and tumor size.

§Adjusted for age, race, Quetelet (body mass) index, tumor size, and number of positive lymph nodes.

Discussion

Breast cancer patients who had used estrogen replacement therapy experienced reductions in breast cancer mortality, which waned with time since diagnosis. These reductions in mortality were not due to differences between hormone users and nonusers in tumor size, race, age at diagnosis, Quetelet index, tumor histology, or number of positive lymph nodes. Our results are consistent with some *(9–11,26,27)*, but not all *(13–16)*, other studies of this topic, although others have not examined the results by lymph node status or over such a long period of follow-up. Our results are not directly-comparable to those from studies of hormone use and breast cancer mortality in women without breast cancer, because results from such studies reflect both incidence and survival *(2–8,12)*.

The converging of the hazard rates over time since diagnosis in hormone users and nonusers may reflect selection effects due to variation in the risk of breast cancer mortality among individuals according to hormone use. Thus, a larger proportion of hormone nonusers may have died early because they had tumors with adverse prognostic factors for which we were unable to adjust, with the surviving individuals being at low risk, while a larger proportion of hormone users may have died later because they had tumors with more favorable prognostic factors *(28)*. The longer median times to death for those who died of breast cancer among hormone users than among nonusers are consistent with this explanation. Potentially important prognostic factors for which we were unable to adjust include the degree of tumor differentiation *(15,29)*, the aneuploidy of the tumors *(16,29)*, and the hormone receptor status of the tumors *(30)*. It is also possible that the delay in death from breast cancer in hormone users, who usually stopped taking hormones at the time of diagnosis, is similar to the regression sometimes seen upon stopping treatment of breast cancer with pharmacologic doses of estrogens when the disease progressed *(31)*.

Several methodologic issues need to be considered in interpreting our results. Although the ascertainment of cases during a breast cancer screening program minimized differences in screening between hormone users and nonusers, it is still possible that differences in surveillance before or during the screening program could have confounded our results. This is particularly true among those with lymph node-positive breast cancer because we did not have information on distant metastases at diagnosis.

The absence of information on treatment is another potential concern. If current or past hormone replacement therapy is associated with the use of beneficial treatment regimens but does not itself favorably affect the carcinogenic process, our finding of a reduction in mortality would be misleading. If, however, hormone replacement therapy renders the tumor more responsive to treatment (i.e., to adjuvant endocrine therapy) or otherwise favorably affects the carcinogenic process, our basic finding of a reduction in mortality is valid. However, the magnitude of the reduction in risk due solely to the effect of the hormones is unclear.

Further research is needed to assess the extent to which reductions in breast cancer mortality associated with use of hormone replacement therapy at or prior to breast cancer diagnosis reflect biologic differences in tumors between hormone users and nonusers, an effect of hormones on tumor growth, or some other explanation, such as treatment differences. The effects on breast cancer mortality of continuing or initiating hormone replacement therapy after a breast cancer diagnosis also need to be resolved.

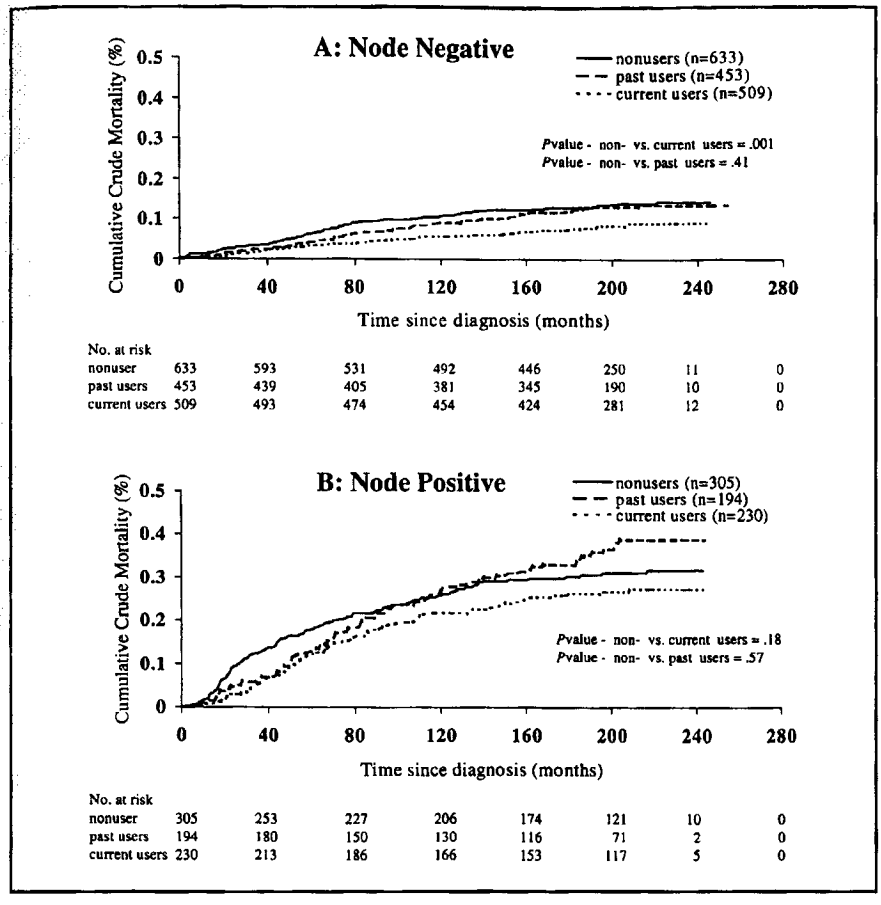

Fig. 1. Unadjusted cumulative crude breast cancer mortality (%) according to axillary lymph node status at diagnosis for nonusers, past users, and current users of estrogen replacement therapy. *P* values are two-sided and statistically significant for $P<.05$. **A)** Women with lymph node-negative disease. Cumulative crude mortality for nonusers at 80, 160, and 240 months = 0.09 (95% confidence interval [CI] = 0.07–0.11), 0.12 (95% CI = 0.10–0.15), and 0.14 (95% CI = 0.12–0.18), respectively; for past users at 80, 160, and 240 months = 0.06 (95% CI = 0.05–0.09), 0.11 (95% CI = 0.09–0.14), and 0.14 (95% CI = 0.10–0.18), respectively; and for current users at 80, 160, and 240 months = 0.04 (95% CI = 0.03–0.06), 0.07 (95% CI = 0.05–0.09), and 0.09 (95% CI = 0.07–0.12), respectively. **B)** Women with lymph node-positive disease. Cumulative crude mortality for nonusers at 80, 160, and 240 months = 0.22 (95% CI = 0.18–0.26), 0.30 (95% CI = 0.25–0.34), and 0.32 (95% CI = 0.26–0.38), respectively; for past users at 80, 160, and 240 months = 0.18 (95% CI = 0.14–0.23), 0.32 (95% CI = 0.26–0.38), and 0.39 (95% CI = 0.31–0.47), respectively; and for current users at 80, 160, and 240 months = 0.16 (95% CI = 0.12–0.21), 0.25 (95% CI = 0.20–0.30), and 0.27 (95% CI = 0.22–0.34), respectively.

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NOTE

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